Docket No. JAB1705USPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Sean Lilienfeld et al.	
Serial No.	:	10/510,314	Art Unit: 1616
Filed	:	October 1, 2004	Examiner: Choi, Frank I.
For	:	STATIN THERAPY FOR ENHANCING COGNITIVE MAINTENANCE	

I hereby certify that this correspondence is being transmitted via The Office electronic filing system in accordance with 37 CFR 1.6(a)(4)

July 9, 2007
(Date of Transmission)

Mary A. Appollina

(Name of applicant, assignee, or Registered Representative)

Mary A. Appollina

(Signature)
July 9, 2007

(Date of Signature)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOAN AMATNIEK, M.D. UNDER 37 C.F.R § 1.132

I, Joan Amatniek, declare as follows:

1) I am a citizen of the United States and hold the position of Director at Ortho-McNeil Janssen Scientific Affairs ("OMJSA").

2) I did my undergraduate studies in History and Science at Harvard College where I received a Bachelor of Arts degree, *magna cum laude* in 1979. I did postgraduate studies at the University of Sussex (England) where I a received Master of Science Degree in History and Social Studies of Science in 1980, and at Columbia University, Graduate School of Journalism, where I received a

Master of Science degree in 1983. I did my medical studies at Albert Einstein College of Medicine where I received a Doctor of Medicine degree with distinction in Epidemiology in 1992. I completed additional graduate studies at Columbia University, Graduate School of Public Health, where I received a Master of Science degree in Epidemiology in 1998.

3) Since completing my Medical Degree, I have held the following positions:

1992-1993: Medicine Intern, Montefiore Medical Center;

1993-1996: Neurology Resident/Assistant Instructor Hospital of the University of Pennsylvania;

1996-1998: Neurology Postdoctoral Clinical Fellow/Clinical Assistant, conducted research in epidemiology of stroke, epilepsy, neurocysticercosis, and Alzheimer's disease with clinical specialization in epilepsy and electroencephalography, Columbia University;

1997-1998: Neurology Assistant Attending, reader of electroencephalograms, Harlem Hospital Center;

1999-present: Joined Janssen Pharmaceutica, Inc. (the predecessor of Janssen Medical Affairs, LLC, Ortho-McNeil Neurologics, Inc., and now OMJSA) in 1999 as Associate Director of Medical Affairs. Promoted to Director, in August 2001.

4) I am a member of the American Academy of Neurology (associate), the American Medical Association, the American Medical Women's Association, and the National Association of Science Writers. I have been a co-author on 30 papers or abstracts and posters that have been published in peer-reviewed journals or presented at scientific symposia and conferences.

5) I have read and understood the specification and claims of United States Patent Application Number 10/510,314 (hereinafter, the "'314 patent application") and the Office Action pertaining to it mailed January 11, 2007.

6) As part of my duties at OMJSA, I presently direct the design, coordination, analysis, and interpretation of clinical studies on galantamine hydrobromide (Razadyne^{TM}). I was a member of a team which was assembled beginning during the summer of 2001 to analyze the early

galantamine pivotal clinical trials for Razadyne™ immediate release ("IR") product (GAL-INT-1, GAL-USA-1 and GAL-USA-10) regarding efficacy of statin use in the treatment of Alzheimer's disease ("AD"). A summary of this work, the "Early IR Analyses", was published earlier this year in: B. Winblad, et al., *Effects of Statins on Cognitive Function in Patients with Alzheimer's Disease in Galantamine Clinical Trials*, Drugs Aging 2007; 24(1); 57-61. A copy of this article is attached hereto as Exhibit A. The Early IR Analyses identified the utility of the combination treatment (galantamine + statin) for Alzheimer's disease and formed the basis of the '314 patent application. The Early IR Analyses, besides including only the original IR trials, also differed from the later analyses that are presented and discussed beginning in paragraph 7, below, in that only the 6-month double blind data were analyzed, and patients who initiated statins after baseline in each of the statin groups were included. Starting in January 2007, I oversaw the conduct of additional post hoc analyses of the early galantamine pivotal clinical trials for Razadyne™ IR product, GAL-INT1, GAL-USA-1 and GAL-USA-10, to assess whether there is an association between the use of statins + galantamine and maintenance of cognitive function in patients diagnosed with AD and whether the effect was synergistic (i.e., meaning more than additive than the effect of each of the compounds separately). Also starting in February 2007, I oversaw the conduct of post hoc analyses of the GAL-INT-10 clinical trial of the Razadyne™ extended release ("ER") product, which also included an IR group, to assess whether there is an association between the use of statins + galantamine and maintenance of cognitive function in patients diagnosed with AD and whether the effect was synergistic. These analyses were conducted to further evaluate the clinical meaning of the unexpected findings of the Early IR Analyses. As discussed in detail below, data from these clinical trials show that, surprisingly and unexpectedly, there were strong signals of both a short-term and a sustained positive synergistic effect on cognitive function in the patients receiving galantamine and statins at the same time, possibly involving both symptomatic and disease modifying effects.

<u>Post hoc Analyses: Initial Pivotal Trials Galantamine IR</u>

7. Post hoc analyses were conducted on data pooled from three (one 5-month and two 6-month) double blind, placebo-controlled, clinical trials of galantamine IR in patients with AD, GAL-INT-1, GAL-USA-1 and GAL-USA-10, which were the pivotal trials for the original galantamine product, galantamine IR. (Data from after the initial double blind period was

collected during open label extensions.) Galantamine IR was dosed twice a day with forced titration to 24 mg by week 3 in 2 of the trials; while current labeling specifies a slower dose titration from 8 mg to 16 mg after 4 weeks with an optional titration to 24 mg after at least 4 more weeks of treatment. Patients had been randomized to galantamine or placebo and then in the post-hoc analyses were stratified by statin into four treatment groups: galantamine + statin, galantamine alone, placebo + statin, and placebo alone . Only the 24 mg galantamine treatment group was used because this dosing level was used across all three trials, generating the dose with the largest number of galantamine + statin users. Post-baseline statin initiators were excluded. The most frequently used statin was simvastatin, but also used in descending order of frequency were pravastatin, lovastatin, fluvastatin and atorvostatin. Baseline total cholesterol was similar in each of the four groups.

8. Patient demographics are shown in **Figure 1**. The statin users were slightly more likely to be male, younger, and heavier than the people who did not use statins. Post hoc efficacy was based on the Alzheimer's Disease Assessment Scale cognitive scale (ADAS-cog/11) and intent to treat analyses, the most conservative analysis method for efficacy. The ADAS-cog/11 consists of a battery of test questions administered by a trained clinician. This scale is well validated and is commonly used to assess cognitive function in clinical trials of Alzheimer's disease treatments. On this scale, decreases in score are associated with improved cognitive function. Given that these are post-hoc analyses, the focus is on descriptive rather than statistical results, although p-values are included in the figures. The size of the standard error bars is consistent with sensitivity to the number of subjects in each treatment group. Six month change from baseline efficacy data are presented in **Figure 2**. The ADAS-Cog efficacy rank order was galantamine + statin > galantamine alone > placebo + statin ≥ placebo alone. Additionally, both the galantamine + statin and the galantamine alone groups, on average, showed cognitive improvement compared to baseline, whereas the placebo + statin and the statin alone groups did not, consistent with symptomatic effects for both galantamine + statin and the galantamine alone groups. Moreover, the six month efficacy data clearly shows that when compared to placebo the effect in the galantamine plus statin group on cognitive function is more than additive (i.e., synergistic) as compared to the summed effect of the galantamine alone and placebo + statin groups. In addition, the patients in the galantamine + statin group were above their baseline scores for 4

more months than the galantamine alone group as shown in **Figure 3**. As can be seen in Figure 3, patients receiving galantamine + statin returned to their original cognitive status at approximately 14 months as compared to 10 months for the patients on galantamine alone and 3 months for patients on placebo + statin. Lastly, as can be seen in **Figure 3**, at 18 and 24 months, a sustained efficacy difference in favor of galantamine + statin compared to galantamine alone appears to exist, which is consistent with a synergistic effect, which could be more definitively evaluated if a placebo + statin group was available at 24 months for additive comparisons. Also, qualitatively, the slopes of the galantamine + statin and galantamine alone groups may be interpreted as diverging from each other at approximately month 18, which is consistent with a synergistic and perhaps disease modifying effect of the combination treatment. Efficacy data for the subset of moderate AD patients (MMSE < 18) and mild AD patients (MMSE $\geq$ 18) is presented in **Figures 4** and **5**, respectively.

9. The six-month analyses were repeated for the 8, 16, and 32 mg doses of galantamine (see **Figure 6**). Evidence is suggestive of the presence of a dose response curve through 24 mg of galantamine. However, given the small sample size, the presence of such a curve existing through 32 mg or even higher cannot be excluded.

10. It was surprising and unexpected that the patients receiving galantamine + statin would have a beneficial cognitive effect that was synergistic at the end of the double-blind assessment; would see an improvement of 4 months in the time to return to baseline scores as compared to patients receiving galantamine alone, which is also consistent with synergy; and that the difference between the galantamine + statin and the galantamine alone groups continued, and possibly increased, through the 2 years assessed.

<u>Post hoc Analyses: GAL-INT-10</u>

11. Post hoc analyses were conducted on the 6-month double-blind, placebo-controlled trial of extended- and immediate-release formulations of galantamine in mild to moderate AD, GAL-INT-10. Galantamine IR was dosed twice a day; galantamine ER was dosed in the morning with evening placebo. This trial utilized a slower dose titration schedule (dose escalation after 4 weeks), which was and is consistent with present labeling, and flexible titration to 24 mg based on the clinical judgment of the investigator. In the post hoc analyses, each of the galantamine ER

24 mg and the galantamine IR 24 mg arms, patients were divided into four treatment groups: galantamine + statin, galantamine alone, placebo + statin, and placebo alone. Post-baseline statin initiators were excluded. The most frequently used statin was atorvostatin, but also used in descending order of frequency were simvastatin, pravastatin, lovastatin and fluvastatin. For the ER 24 mg group, patient demographics are shown in **Figure 7**. Post hoc efficacy was based on the ADAS-cog/11 and intent to treat analyses, unless otherwise specified. Given that these are post-hoc analyses, the focus is on descriptive rather than statistical results, although p-values are included in the figures. The size of the standard error bars is consistent with sensitivity to the number of subjects in each treatment group. Six month efficacy data for the ER 24 mg group is presented in **Figure 8** and clearly shows that the effect on cognition in the galantamine ER + statin group is more than additive (i.e., synergistic) as compared to sum of the effects of the galantamine ER alone and placebo + statin groups. The ADAS-Cog efficacy rank order was galantamine ER + statin > galantamine ER alone > placebo + statin ≥ placebo alone. Efficacy data for the subset of moderate AD patients (MMSE < 18) and mild AD patients (MMSE ≥ 18) is presented in **Figures 9** and **10**, respectively. The effect of the combination therapy of galantamine ER 24 + statin remained synergistic. The analyses on the long-term data regarding time to cross baseline and the slopes have yet to be conducted.

12. For the IR 24 mg group, patient demographics are shown in **Figure 11**. Six-month efficacy data for the IR 24 mg group is presented in **Figure 12**. In this patient population, the ADAS-Cog efficacy rank order was galantamine alone > galantamine + statin > placebo + statin ≥ placebo alone. However, when the completer population was examined for the IR 24 mg data, the ADAS-Cog efficacy rank order was consistent with the analyses above: galantamine + statin > galantamine alone > placebo + statin ≥ placebo alone (see **Figure 13**). Moreover, the effect of the combination therapy of galantamine IR 24 and statins was synergistic in the completer population. The analyses on the long-term data regarding time to cross baseline and the slopes have yet to be conducted.

13. The most commonly used statin in the earlier trials (INT-1, USA-1, and USA-10) was simvastatin while in GAL-INT-10 the most commonly used statin was atorvastatin, which may in part be why, given that simvastatin purportedly crosses the blood-brain-barrier more easily than atorvastatin, a more robust synergistic effect was seen in the earlier trials from the combination

treatment. This is consistent with the concept that the more galantamine and statin are present simultaneously, the more synergistic the effect.

Conclusion

14. In conclusion, data from the above-described clinical trials show that, surprisingly and unexpectedly, there was a synergistic positive effect on cognitive function in the patients receiving galantamine + statin, as compared to those receiving either galantamine or placebo + statin. Additionally, the data from the initial pivotal trials, unexpectedly and surprisingly, showed that the patients receiving galantamine + statin were above their baseline scores for 4 more months compared to the patients receiving galantamine alone, which is consistent with a synergistic effect as well. Furthermore, the sustained difference in level of efficacy of galantamine + statin versus galantamine alone to the end of the analyses at 24 months, was surprising and unexpected as well. These synergistic effects, potentially both symptomatic and disease modifying, would not be expected by one of ordinary skill in the art, as was apparent when the data were presented under confidentiality agreement to nine experts in the field of statins, galantamine, and Alzheimer's disease during the first two weeks of June 2007.

15. All statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. All statements in this declaration are made with the knowledge that willful false statements and the like if made in this declaration are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code, and that any willful false statement may jeopardize the validity or enforceability of any patent that may issue on the application for which this declaration is made.

Dated this 3rd day of July, 2007

Joan Amatniek, M.D.

Exhibit A

Drugs Aging 2007; 24 (1): 57-61
1170-229X/07/0001-0057/$44.95/0

Effects of Statins on Cognitive Function in Patients with Alzheimer's Disease in Galantamine Clinical Trials

Bengt Winblad,[1] *Vesna Jelic*,[1] *Paul Kershaw*[2] and *Joan Amatniek*[3]

1 Alzheimer Disease Research Center and Department of Clinical Geriatrics, Karolinska Institute, Stockholm, Sweden
2 Johnson & Johnson Pharmaceutical Services, Raritan, New Jersey, USA
3 Ortho McNeil Neurologics, Inc., Titusville, New Jersey, USA

Abstract

Background and objective: A number of reports have been published on the possible involvement of changes in brain cholesterol metabolism in the origin of Alzheimer's disease (AD) and the potential for influencing these changes by administration of HMG-CoA reductase inhibitors ('statins'). The aim of this study was to evaluate a potential association between use of statins and maintenance of cognitive function in patients with AD in galantamine clinical trials.

Method: A *post hoc* analysis was conducted on data pooled from three double-blind, placebo-controlled, clinical trials of galantamine in patients with AD. Patients were divided into four treatment groups: statin plus galantamine (n = 42), statin alone (n = 50), galantamine alone (n = 614) or neither galantamine nor statin (n = 619).

Results: Galantamine was associated with a significant beneficial effect on cognitive status ($p < 0.001$). The association of use of statins with changes in cognitive status was not significant ($p = 0.083$). There was no significant interaction between the effects on cognition of statins and galantamine ($p = 0.183$) and no statistically significant changes in adverse effect rates were observed.

Conclusion: These findings suggest the need for larger long-term trials to confirm or refute possible effects of statins on cognitive function and the potential interaction of statins with acetylcholinesterase inhibitors in the treatment of AD.

Background and Objective

A number of reports have been published on the possible involvement of changes in brain cholesterol metabolism in the origin of Alzheimer's disease (AD)[1,2] and the potential for influencing these changes by administration of HMG-CoA reductase inhibitor drugs, commonly known as statins.[3] Cholesterol may play a role in the formation and accumulation of β-amyloid (Aβ) in the brain tissue of patients with AD. Refolo and colleagues[4] reported that a diet high in cholesterol increases Aβ accumulation and AD-related pathology in the transgenic-mouse model, with relatively little change in brain cholesterol. Feeding a high-cholesterol diet to rab-

bits has also produced Aβ deposits in the hippocampus.[5]

Consistent with these findings are the results of several epidemiological investigations that have suggested that statin administration might be associated with slowing of cognitive decline.[6-9] On the other hand, two large, randomised trials of statins in patients at high risk for cardiovascular disease (the PROSPER [PROspective Study of Pravastatin in the Elderly at Risk] trial[10] and the Heart Protection Study[11]), which included assessment of the effects of statins on cognitive function, showed no evidence of such effects. Nevertheless, review articles, including a Cochrane review, have pointed out the plausibility of a beneficial effect of statins in preventing or slowing AD, while noting that the evidence is insufficient to confirm this effect.[12-15]

The primary purpose of the present *post hoc* analysis is to assess whether there is an association between use of statins and maintenance of cognitive function in patients diagnosed with AD. A secondary purpose is to assess the safety of treating AD patients with a statin in combination with the acetylcholinesterase inhibitor (AChEI) galantamine.

Methods

Data were combined from one 5-month and two 6-month double-blind, placebo-controlled, clinical trials in which a total of 1325 patients with AD were assigned to treatment with galantamine 24 mg/day or placebo. These studies were conducted in multiple outpatient treatment settings in Europe, Canada and the US, using very similar inclusion and exclusion criteria to evaluate the efficacy, safety and tolerability of galantamine.[16-18] In this sub-analysis of pooled data, patients were categorised based on their use of galantamine or use of statins as a permitted, stably prescribed concomitant medication in these trials. Drug treatment groups were compared at baseline with respect to gender, age, total cholesterol level and cognitive status as reflected by baseline scores on the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11) and the Mini-Mental State Examination (MMSE). Change in ADAS-cog/11 score was used to assess treatment efficacy.

Safety was assessed by calculating rates of adverse events commonly associated with AChEIs[19] (including nausea, vomiting, diarrhoea and anorexia, as well as gastrointestinal symptoms overall), statins[20] (including back pain, leg cramps, leg pain, muscle atrophy, muscle weakness, myalgia, skeletal pain and other musculoskeletal symptoms) and with both AChEIs and statins (including abdominal pain and headache). To assess adverse events associated with AChEIs, the statin + galantamine group was compared with the galantamine-alone group; to assess adverse events associated with statins, the statin + galantamine group was compared with the statin-alone group; and to assess adverse events associated with both AChEIs and statins, the statin + galantamine group was compared with the galantamine-alone and statin-alone groups.

Statistical Methods

The χ^2 test was used to compare characteristics of the treatment groups with regard to categorical variables, and ANOVA was used to compare continuous variables. Treatment efficacy data were analysed using intent-to-treat analysis. The groups were compared with regard to treatment efficacy using ANOVA with terms for statin use, galantamine treatment, and the interaction of statin and galantamine. In addition, the ANOVA controlled for study and mild AD (in terms of severity), based on MMSE scores ≥18. To compare designated treatment groups with respect to safety data, relative risks (RRs) of adverse events were calculated with 95% CIs.

Results

The patients were divided into four treatment groups: statin + galantamine (n = 42), statin alone (n = 50), galantamine alone (n = 614) and neither statin nor galantamine (n = 619). The characteristics of the groups are shown in table I. There were no significant differences among the groups with regard to baseline cognitive scores or total cholesterol levels. The patients in the statin + galantamine group

Table I. Characteristics of treatment groups[a]

Variable	Statin + galantamine (n = 42)	Statin alone (n = 50)	Galantamine alone (n = 614)	Neither statin nor galantamine (n = 619)	p-Value
Gender (% female)	47.6	58.0	66.3	63.0	0.063
Age (y)	72.4 (8.4)[b]	74.0 (7.8)	75.7 (7.9)	75.2 (8.2)	0.045
Baseline ADAS-cog/11 score	26.8 (11.3)	25.7 (8.9)	26.5 (10.1)	26.8 (10.6)	0.852
Total cholesterol (mg/dL)[c]	218.0 (47.2)	219.3 (38.1)	228.3 (43.6)	224.6 (43.8)	0.177
Baseline MMSE score	18.2 (4.1)	18.4 (3.8)	18.7 (3.8)	18.7 (4.0)	0.784
AD severity (% mild)[d]	61.9	66.0	64.8	64.9	0.98

a Values are expressed as means (SD) unless otherwise indicated.

b Pairwise comparisons significant at $p < 0.05$ for statin + galantamine versus galantamine alone, and for statin + galantamine versus neither statin nor galantamine.

c Data available for 1311 patients only.

d Mild (MMSE ≥18) compared with moderate (MMSE <18).

AD = Alzheimer's disease; **ADAS-cog/11** = 11-item Alzheimer's Disease Assessment Scale – cognitive subscale; **MMSE** = Mini-Mental State Examination.

were significantly younger than those receiving galantamine alone and those receiving neither statin nor galantamine ($p < 0.05$). The statin groups (statin alone and statin + galantamine) had fewer females than the non-statin groups (galantamine alone and neither statin nor galantamine); however, the difference was not statistically significant ($p = 0.06$).

The statins prescribed were simvastatin, pravastatin, lovastatin, fluvastatin and atorvastatin. The distribution of statins did not differ significantly between the statin + galantamine and statin-alone groups.

The changes in ADAS-cog/11 scores from baseline to the end of treatment are shown in table II. The galantamine-alone and statin + galantamine groups experienced improvements in cognitive status. Conversely, both the statin-alone and neither statin nor galantamine groups experienced a decline in cognitive status. Galantamine was associated with a significant beneficial effect on cognitive status ($p < 0.001$). The association between use of statins and change in cognitive status was not significant ($p = 0.083$). There was no significant interaction between the effects on cognition of statins and galantamine ($p = 0.183$). These results were derived from ANOVA calculations, controlling for study and AD severity based on MMSE.

Table II. Changes in cognitive status.[a] Negative values on 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11) reflect improved cognitive status

	Statin + galantamine (n = 42)	Statin alone (n = 50)	Galantamine alone (n = 614)	Neither statin nor galantamine (n = 619)
Change in ADAS-cog/11 score	−2.85 (0.91), p = 0.183	1.98 (0.85), p = 0.083	−0.88 (0.25), p < 0.001	2.24 (0.24)

a Values are expressed as least square means with standard errors in parentheses.

The assessment of safety with regard to adverse events commonly associated with AChEIs showed that, compared with treatment using galantamine only, administering a statin and galantamine simultaneously may have increased the likelihood of diarrhoea (RR 1.79; 95% CI 0.81, 3.94) and abdominal pain (RR 1.62; 95% CI 0.61, 4.35), although in both instances the 95% CIs included a value of 1. In terms of adverse events commonly associated with statins, compared with statin-only treatment, combining a statin and galantamine elevated the risk of musculoskeletal pain (RR 2.78; 95% CI 0.77, 10.08). No myopathy was reported in these trials. Because all 95% CIs included a value of 1, none of the elevations in RR was statistically significant.

Discussion

Cognitive function improved significantly with the administration of galantamine 24 mg/day. Adding a statin to the treatment regimen with ga-

lantamine did not have a statistically significant effect on changes in cognitive function compared with galantamine treatment alone, although the combination treatment showed numerically greater improvement. Treatment with a statin without concomitant use of galantamine in these trials was not associated with statistically significant improvement in cognitive function in patients with AD; however, a very small numerical difference in favour of statin administration alone was apparent compared with patients who received neither a statin nor galantamine.

Although statins may some day play a role in the prevention of AD, as the findings of several epidemiological and mechanistic studies appear to suggest,[1] this *post hoc* analysis has not proven that statins with or without the use of an AChEI contribute to treatment of already established AD. However, the results of this analysis, although not statistically significant, are promising in view of the fact that some numerical trends emerged despite the small sample size. Future studies with more patients may help to elucidate these findings.

To establish a 2-point difference in score change on the ADAS-cog/11 scale over the study period, which would be clinically significant, the population taking statins would have to be much larger than that of the present analysis. The short duration of these trials exacerbates the sample-size issue because the anticipated change in cognition in placebo patients during this time is small. Because inadequate statistical power increases the likelihood of non-significant findings being observed and the risk of type II statistical errors, these results must not be over-interpreted. However, the present data, which were obtained within the context of three large studies of galantamine administration, will at least be important in justifying additional research. Future studies also should take into account potential co-variates and risk factors associated with co-morbid illnesses and concomitant therapies, as well as the type of statin and its bioavailability.

The safety assessment with respect to giving patients both statin and galantamine therapy showed that this combination may increase the point estimate of RR of certain adverse events that have been associated with either AChEIs or statins. However, in this pooled analysis, the difference in risk was not statistically significant. Here, too, the relatively small size of the statin + galantamine treatment group indicates that further investigation is needed to confirm these findings.

In summary, there are several important limitations to this study:

- The sub-analysis is based on a non-random sample of pooled subjects with regard to statin use, resulting in baseline differences between the statin and non-statin treatment groups with respect to age and gender proportions.
- The original trials were not designed to ensure sufficient statistical power to assess the effects of statins.
- Administration of statins was heterogeneous with respect to specific statin, dose and treatment duration.
- Follow-up was limited to 5 or 6 months, depending on the clinical trial, which is sufficient for detecting effects of AChEIs compared with placebo but may be insufficient for comparing effects of statins and AChEIs.

An important strength of the current study was that baseline cognitive status within the statin groups was similar to that of the non-statin groups. Additionally, this study represents further assessments of the relationship between statins and AD progression.[21,22]

Conclusions

The present findings, although not conclusive, are suggestive of a potential role for statins in contributing to the maintenance of cognitive function for short periods (5–6 months) in patients diagnosed with AD. Although concerns may be raised over the borderline increased risk of certain adverse events when a statin and galantamine are combined, the overall safety profile of the galantamine + statin combination was similar to the profiles of either drug administered alone; and in all cases, the RR of an increase in adverse events was not statistically significant ($p > 0.05$). Additional studies of longer

duration and with larger numbers of patients taking statins and AChEIs are needed to confirm any potential benefits of statin treatment in patients with AD, alone or in combination with AChEIs.

Acknowledgements

Dr Bengt Winblad is a consultant to Janssen Cilag and Johnson & Johnson, and has taken part in advisory board meetings for and/or received honoraria from Janssen Cilag, Novartis, Pfizer, Merz, Lundbeck, Sanofi, Wyeth, Merck, Sharp and Dohme, and Myriad. Drs Joan Amatniek and Paul Kershaw are employees of Johnson & Johnson. Dr Vesna Jelic has no potential conflicts of interest that are directly relevant to the content of this study.

Drs Winblad, Jelic, Amatniek and Kershaw designed the *post hoc* analysis. The statistical analysis was performed at Janssen Pharmaceutica. Drs Winblad, Jelic, Amatniek and Kershaw provided interpretation of the data and jointly prepared and reviewed the manuscript.

The authors thank Elane M. Gutterman, PhD, and Jeffrey S. Markowitz, DrPH, for performing the statistical analyses and providing valuable comments.

Johnson & Johnson Pharmaceutical Research & Development funded the galantamine clinical trials. Ortho McNeil Neurologics provided funding assistance for the preparation of this article.

References

1. Kivipelto M, Solomon A, Blennow K, et al., editors. Cholesterol, Alzheimer's disease and statins: proceedings of the 5th Symposium on Aging and Aging Disorders. Stockholm, Sweden, 14-15 April 2005. Acta Neurol Scand Suppl. 2006; 185: 1-120

2. Lutjohann D, von Bergmann K. 24S-hydroxycholesterol: a marker of brain cholesterol metabolism. Pharmacopsychiatry 2003; 36 Suppl. 2: S102-6

3. Vega GL, Weiner MF, Lipton AM, et al. Reduction in levels of 24S-hydroxycholesterol by statin treatment in patients with Alzheimer disease. Arch Neurol 2003; 60: 510-5

4. Refolo LM, Malester B, LaFrancois J, et al. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis 2000; 7: 321-31

5. Sparks DL, Kuo YM, Roher A, et al. Alterations of Alzheimer's disease in the cholesterol-fed rabbit, including vascular inflammation: preliminary observations. Ann N Y Acad Sci 2000; 903: 335-44

6. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001; 322: 1447-51

7. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000; 356: 1627-31

8. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002; 59: 223-7

9. Wolozin B, Kellman W, Ruosseau P, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch Neurol 2000; 57: 1439-43

10. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet 2002; 360: 1623-30

11. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360: 7-22

12. Eckert GP, Wood WG, Muller WE. Statins: drugs for AD? J Neural Transm 2005; 112: 1057-71

13. Kirsch C, Eckert GP, Koudinov AR, et al. Brain cholesterol, statins and Alzheimer's disease. Pharmacopsychiatry 2003; 36 Suppl. 2: S113-9

14. Crisby M, Carlson LA, Winblad B. Statins in the prevention and treatment of Alzheimer disease. Alzheimer Dis Assoc Disord 2002; 16: 131-6

15. Scott HD, Laake K. Statins for the prevention of Alzheimer's disease. Cochrane Database Syst Rev 2001: CD003160

16. Raskind MA, Peskind ER, Wessel T, et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology 2000; 54: 2261-8

17. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology 2000; 54: 2269-76

18. Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. BMJ 2000; 321: 1445-9

19. Gauthier S. Cholinergic adverse effects of cholinesterase inhibitors in Alzheimer's disease: epidemiology and management. Drugs Aging 2001; 18: 853-62

20. Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999; 341: 498-511

21. Simons M, Schwarzler F, Lutjohann D, et al. Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled, double-blind trial. Ann Neurol 2002; 52: 346-50

22. Sjogren M, Gustafsson K, Syversen S, et al. Treatment with simvastatin in patients with Alzheimer's disease lowers both alpha- and beta-cleaved amyloid precursor protein. Dement Geriatr Cogn Disord 2003; 16: 25-30

Correspondence and offprints: Dr *Joan Amatniek*, Ortho McNeil Neurologics, Inc., 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA.

Figure 1

Patient Demographics (ITT)
(GAL-INT-1, GAL-USA-1, GAL-USA-10)

PARAMETERS	GALANTAMINE + STATIN (N=41)	GALANTAMINE ALONE (N=614)	STATIN ALONE (N=44)	PLACEBO (N=619)
GENDER				
FEMALE	19 (46.3%)	407 (66.3%)	25 (56.8%)	390 (63.0%)
MALE	22 (53.7%)	207 (33.7%)	19 (43.2%)	229 (37.0%)
RACE				
BLACK	2 (4.9%)	20 (3.3%)	1 (2.3%)	20 (3.2%)
CAUCASIAN	36 (87.8%)	580 (94.8%)	43 (97.7%)	584 (94.7%)
HISPANIC	1 (2.4%)	8 (1.3%)	0 (0.0%)	7 (1.1%)
ASIAN	1 (2.4%)	2 (0.3%)	0 (0.0%)	3 (0.5%)
OTHER	1 (2.4%)	2 (0.3%)	0 (0.0%)	3 (0.5%)
AGE, YEARS				
MEAN	72.68	75.65	73.80	75.21
SD	8.25	7.90	7.78	8.22
WEIGHT, KG				
NUMBER OF SUBJECTS	41	611	44	613
MEAN	71.91	66.50	69.90	66.80
SD	12.99	13.40	14.20	13.10
DURATION(YR) SINCE DIAG. OF PROB. AD				
NUMBER OF SUBJECTS	41	613	44	618
MEAN	1.17	1.09	1.17	1.12
SD	1.26	1.57	1.74	1.47
MMSE TOTAL SCORE				
MEAN	18.46	18.90	19.20	18.68
SD	4.07	3.80	3.27	3.80

Figure 2

Six Month Efficacy

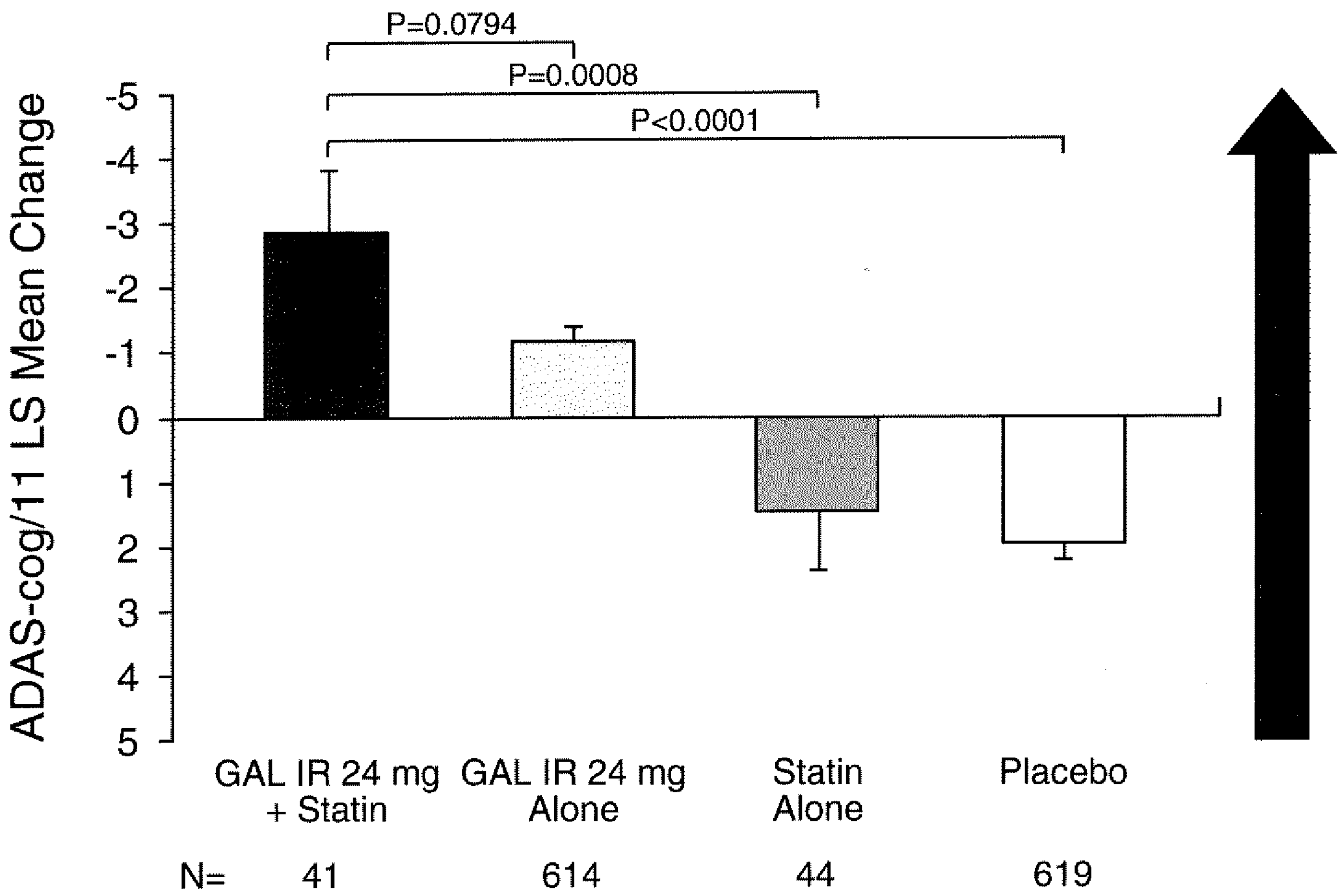

Figure 3

Time to Cross Baseline

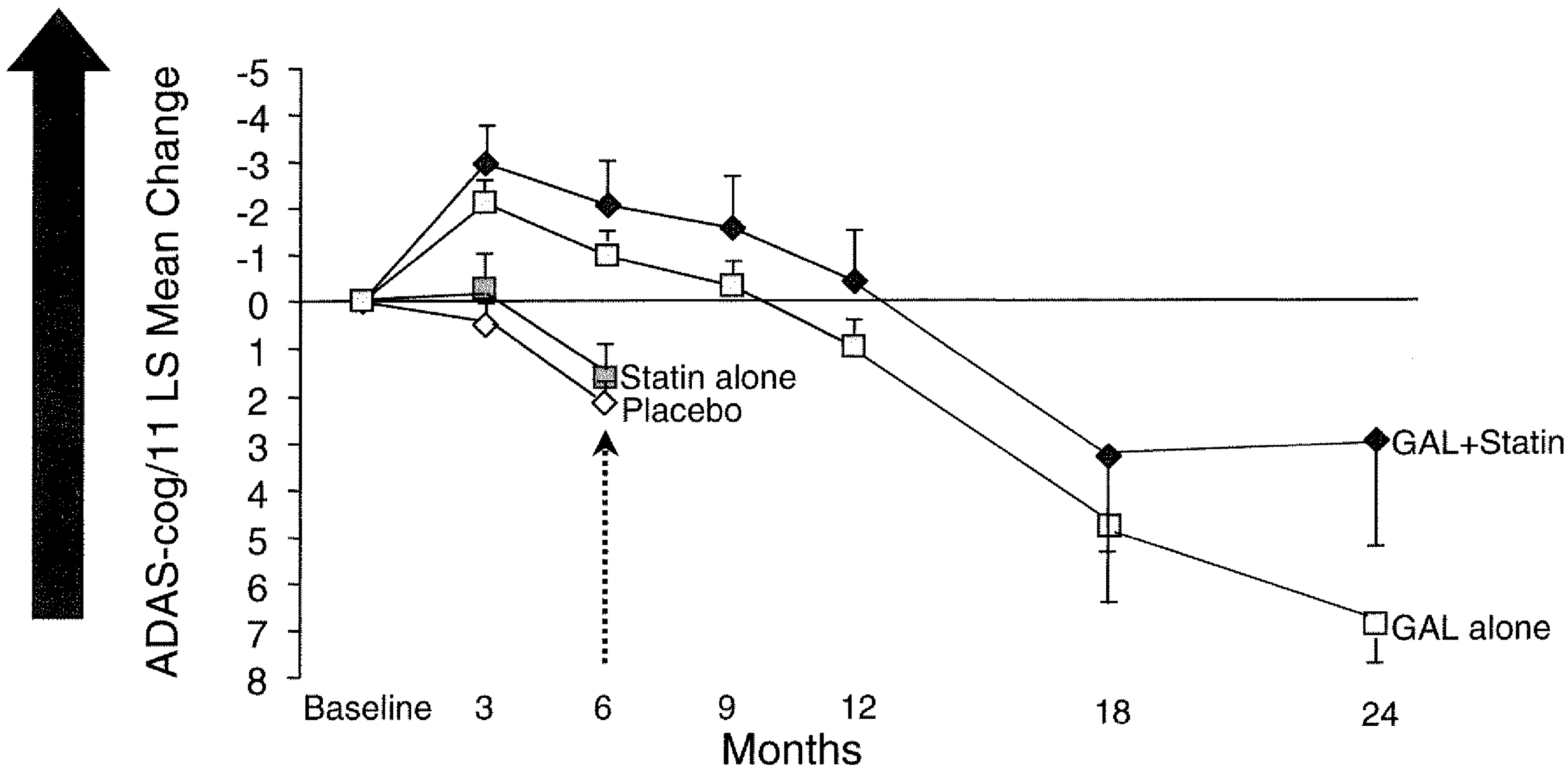

Figure 4

Efficacy in Moderate AD

(MMSE <18)

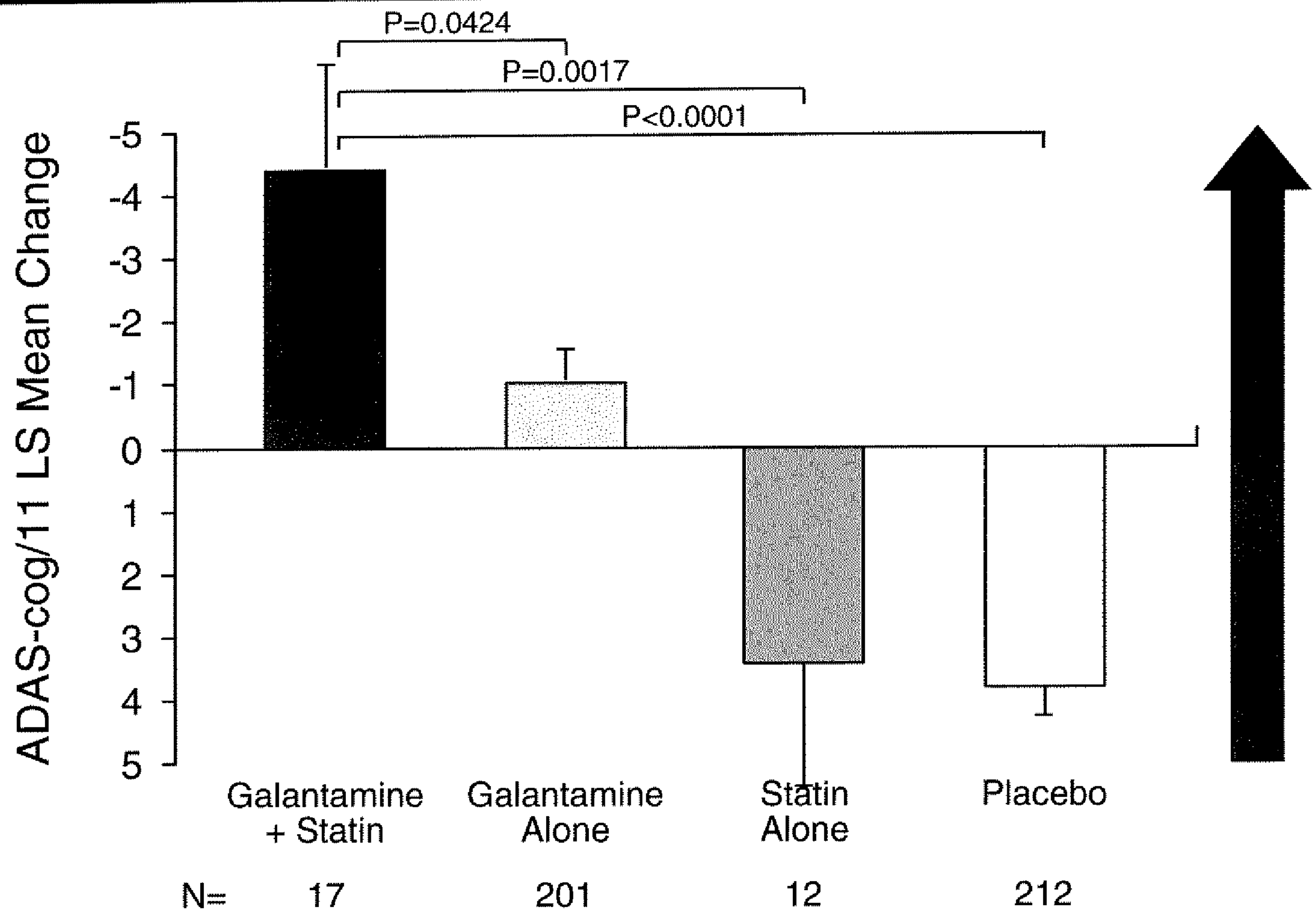

Figure 5

Efficacy in Mild AD

(MMSE ≥18)

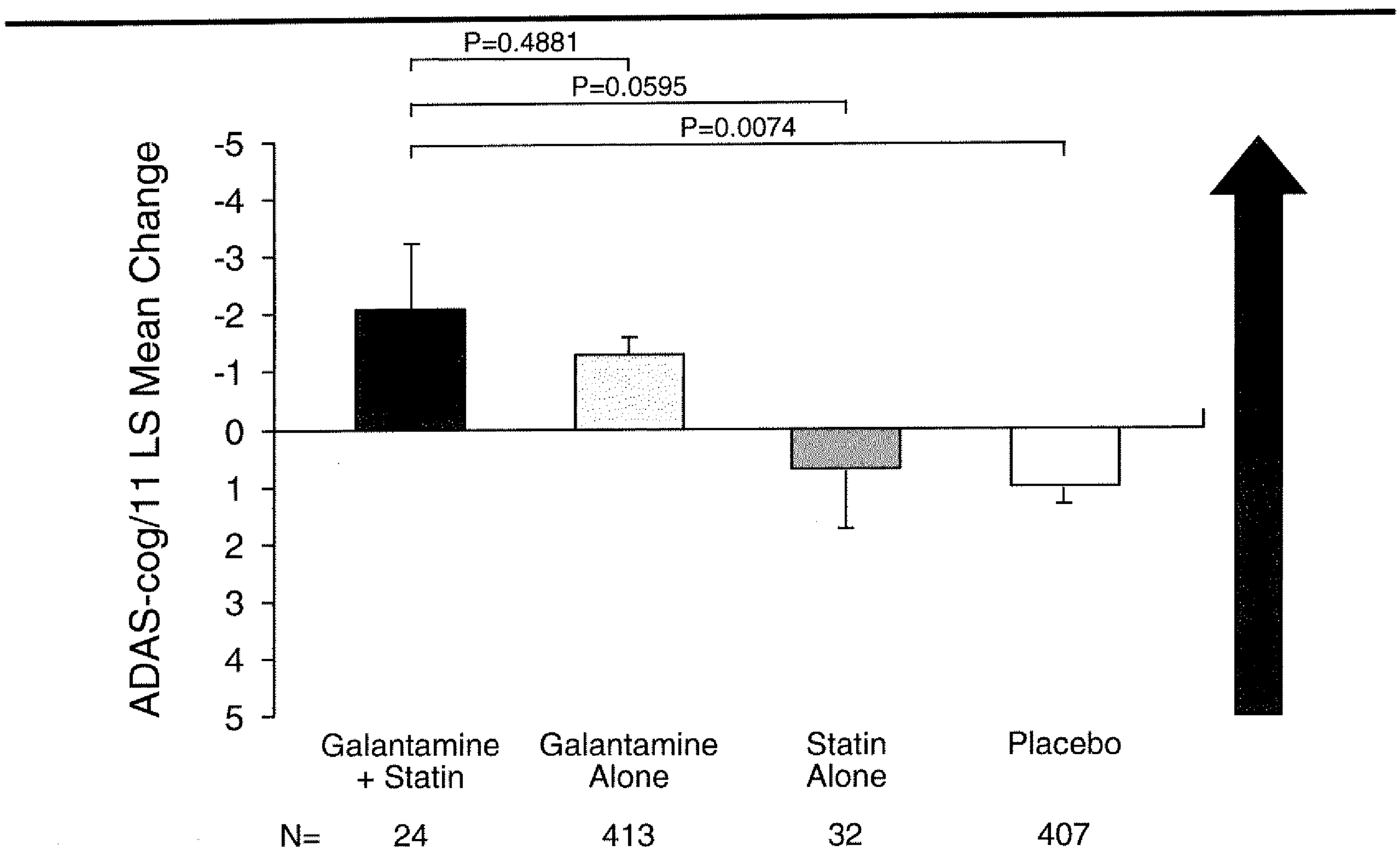

Figure 6

Dose Response

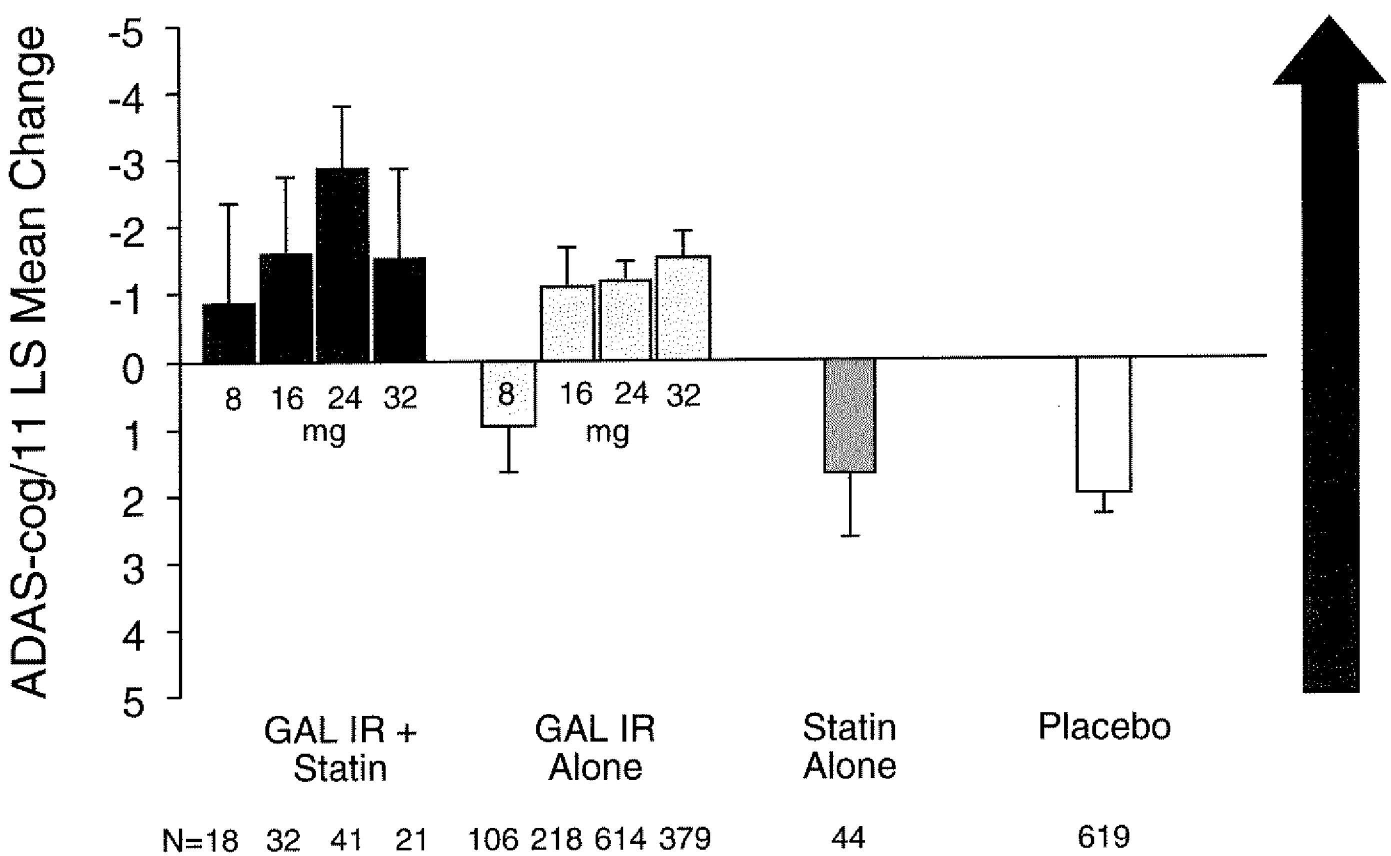

Figure 7

Patient Demographics
(GAL-INT-10, ER 24 mg)

PARAMETERS	GAL CR 24 MG + STATIN (N=36)	GAL CR 24 MG ALONE (N=168)	STATIN ALONE (N=46)	PLACEBO (N=246)
GENDER				
FEMALE	22 (61.1%)	101 (60.1%)	26 (56.5%)	164 (66.7%)
MALE	14 (38.9%)	67 (39.9%)	20 (43.5%)	82 (33.3%)
RACE				
BLACK	0 (0.0%)	6 (3.6%)	3 (6.5%)	8 (3.3%)
CAUCASIAN	36 (100.0%)	156 (92.9%)	41 (89.1%)	222 (90.2%)
HISPANIC	0 (0.0%)	1 (0.6%)	2 (4.3%)	3 (1.2%)
ORIENTAL	0 (0.0%)	3 (1.8%)	0 (0.0%)	7 (2.8%)
OTHER	0 (0.0%)	2 (1.2%)	0 (0.0%)	6 (2.4%)
AGE, YEARS				
NUMBER OF SUBJECTS	36 46	246	168	
MEAN	76.94	75.86	74.46	76.67
SD	5.91	7.94	6.27	8.05
WEIGHT, KG				
NUMBER OF SUBJECTS	36	168	46	245
MEAN	71.14	69.76	71.07	67.25
SD	11.65	15.30	12.26	15.17
DURATION(YR) SINCE DIAG. OF PROB. AD				
NUMBER OF SUBJECTS	36	168	46	246
MEAN	0.75	1.26	1.14	1.28
SD	1.25	1.58	1.37	1.65
MMSE TOTAL SCORE				
NUMBER OF SUBJECTS	36	168	46	246
MEAN	19.47	18.18	17.72	18.24
SD	3.39	3.99	4.32	3.97

Figure 8

Six Month Efficacy
(GAL ER 24mg)

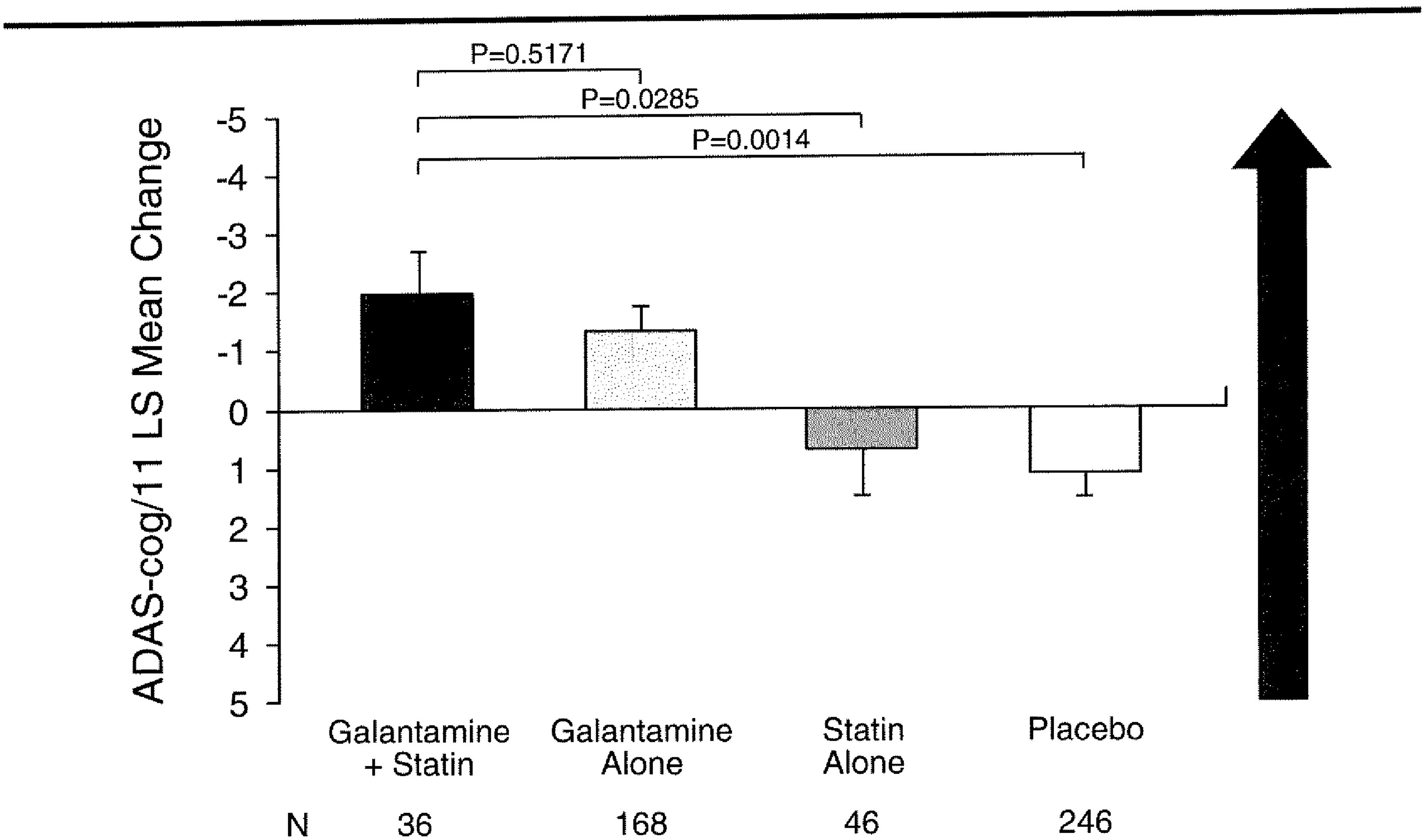

Figure 9

Efficacy in Moderate AD
(GAL ER 24 mg; MMSE <18)

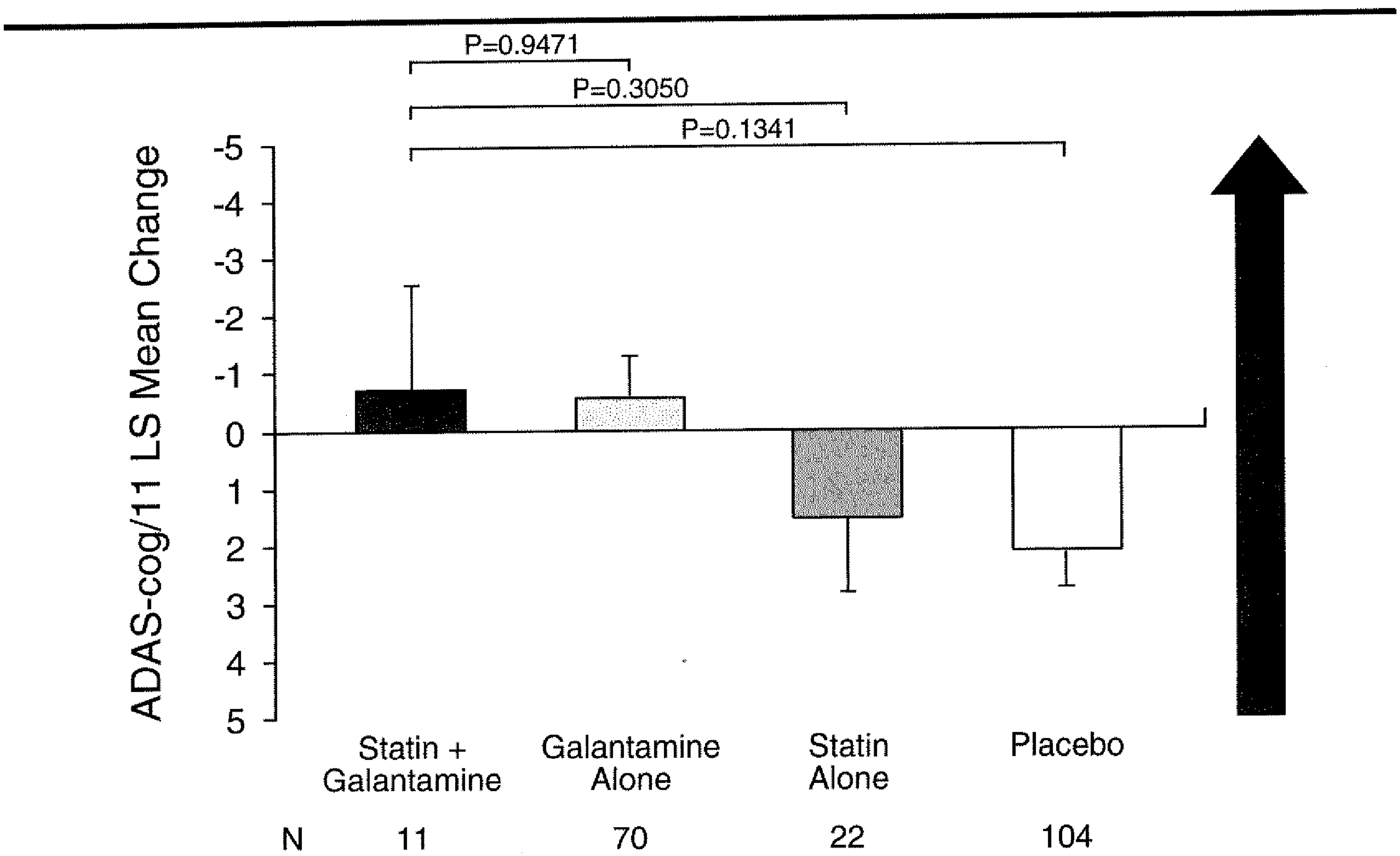

Figure 10

Efficacy in Mild AD

(GAL ER 24 mg; MMSE ≥18)

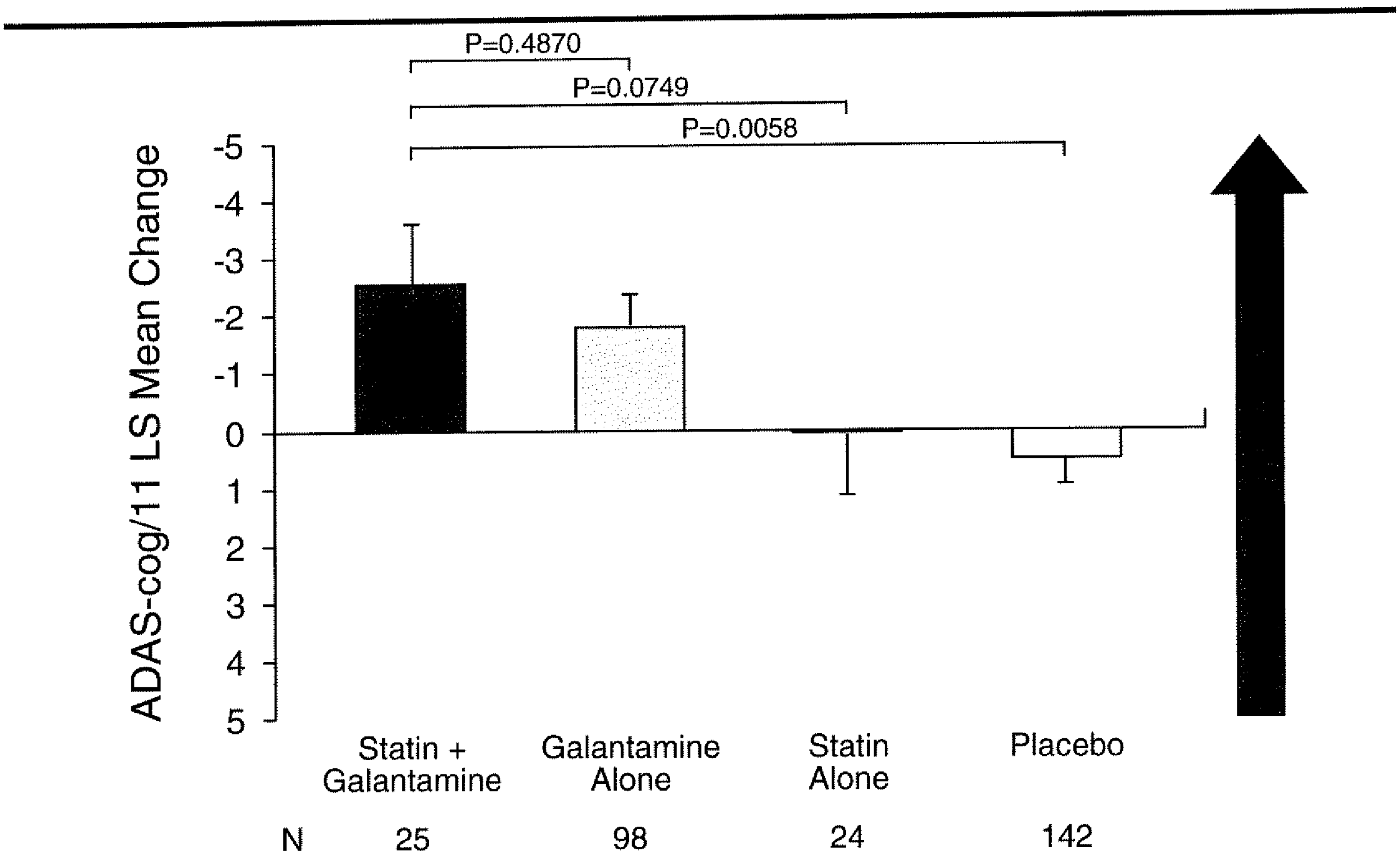

Figure 11

Patient Demographics
(GAL-INT-10, IR 24 mg)

PARAMETERS	GAL IR + STATIN (N=40)	GAL IR ALONE (N=252)	STATIN ALONE (N=46)	PLACEBO (N=246)
GENDER				
FEMALE	19 (47.5%)	160 (63.5%)	26 (56.5%)	164 (66.7%)
MALE	21 (52.5%)	92 (36.5%)	20 (43.5%)	82 (33.3%)
RACE				
BLACK	1 (2.5%)	9 (3.6%)	3 (6.5%)	8 (3.3%)
CAUCASIAN	39 (97.5%)	225 (89.3%)	41 (89.1%)	222 (90.2%)
HISPANIC	0 (0.0%)	4 (1.6%)	2 (4.3%)	3 (1.2%)
ORIENTAL	0 (0.0%)	4 (1.6%)	0 (0.0%)	7 (2.8%)
OTHER	0 (0.0%)	10 (4.0%)	0 (0.0%)	6 (2.4%)
AGE, YEARS				
NUMBER OF SUBJECTS	40	252	46	246
MEAN	75.65	76.33	74.46	76.67
SD	5.36	8.23	6.27	8.05
WEIGHT, KG				
NUMBER OF SUBJECTS	40	251	46	245
MEAN	76.17	67.38	71.07	67.25
SD	15.57	15.78	12.26	15.17
DURATION(YR) SINCE DIAG. OF PROB. AD				
NUMBER OF SUBJECTS	40	252	46	246
MEAN	1.06	1.11	1.14	1.28
SD	1.05	1.41	1.37	1.65
MMSE TOTAL SCORE				
NUMBER OF SUBJECTS	40	252	46	246
MEAN	18.45	17.87	17.72	18.24
SD	4.01	4.06	4.32	3.97

Figure 12

Six Month Efficacy

(GAL IR 24 mg)

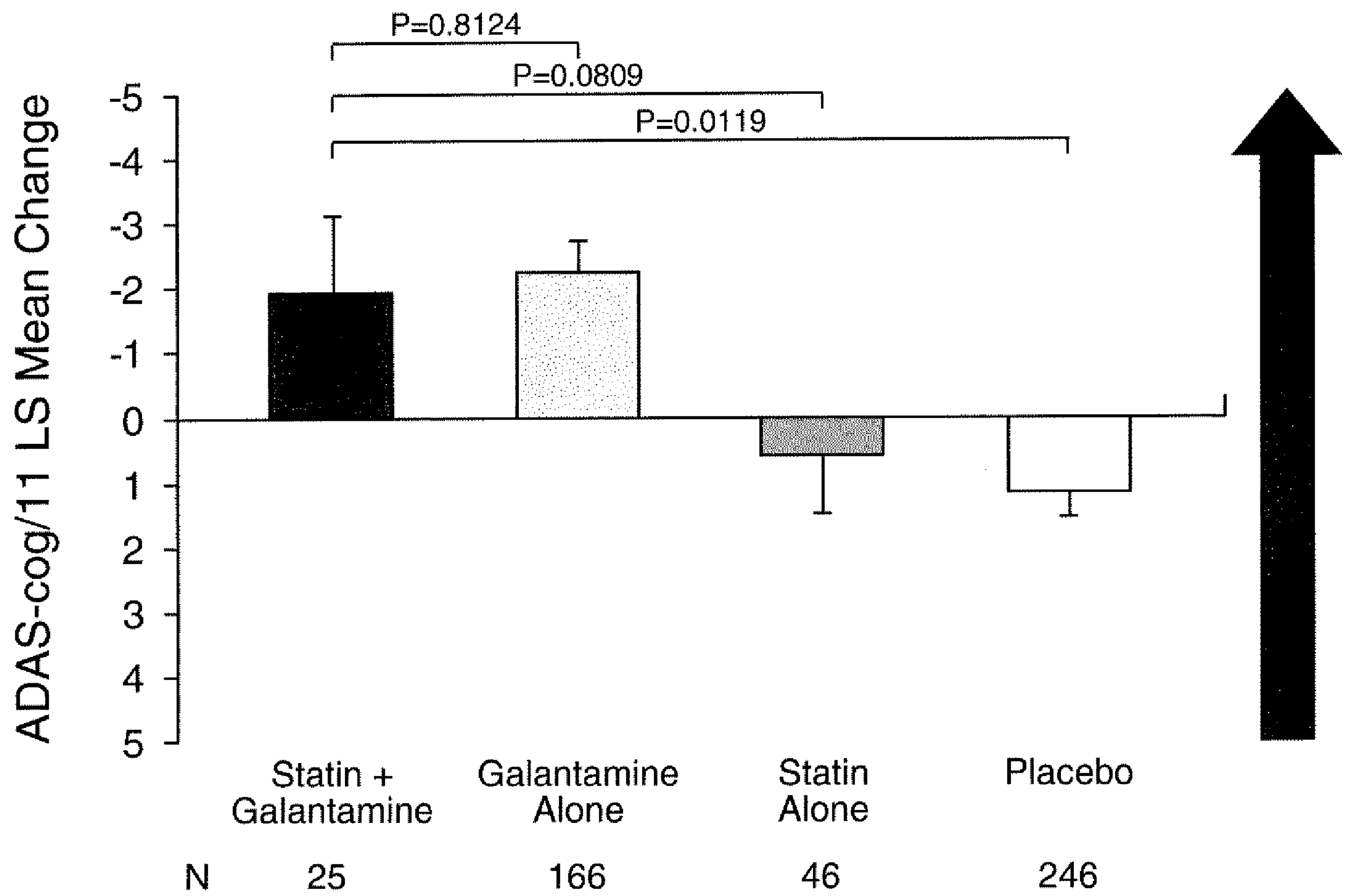

Figure 13

Six Month Efficacy:
Completer Population (GAL IR 24mg)